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Zochios, Vasileios; Parhar, Ken; Vieillard-Baron, Antoinne

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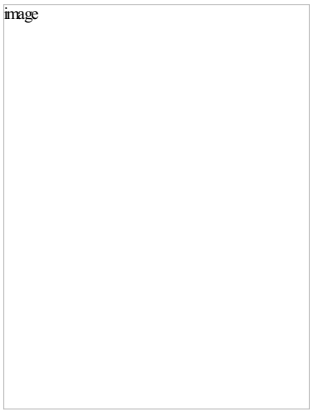

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Title: Protecting the Right Ventricle in ARDS: The Role of Prone Ventilation

Authors: [1] Vasileios Zochios MD, [2] Ken Parhar MD, [3]Antoinne Vieillard-Baron MD, PhD

[1] University Hospitals Birmingham National Health Service Foundation Trust
Department of Critical Care Medicine, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, UK
Perioperative Critical Care and Trauma Trials Group, Institute of Inflammation and Ageing, Centre of Translational Inflammation Research, University of Birmingham, Birmingham, UK
[2] Department of Critical Care Medicine, University of Calgary, Calgary, Canada

[3] Assistance Publique-Hôpitaux de Paris, University Hospital Ambroise Paré, Intensive Care Unit, Section Thorax-Vascular Disease-Abdomen-Metabolism, 92100 Boulogne-Billancourt, France, University of Versailles Saint-Quentin en Yvelines, Faculty of Medicine Paris Ile-de-France Ouest, 78280 Saint-Quentin en Yvelines, France, INSERM U-1018, CESP, Team 5 (EpReC, Renal and Cardiovascular Epidemiology), UVSQ, 94807 Villejuif, France.

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Corresponding author:

Dr Vasileios Zochios MD MRCP (UK)
University Hospitals Birmingham NHS Foundation Trust
Department of Critical Care Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2WB, UK
Perioperative Critical Care and Trauma Trials Group, Institute of Inflammation and Ageing
Centre of Translational Inflammation Research
University of Birmingham, Birmingham, UK
Email: vasileioszochios@doctors.org.uk

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Acute respiratory distress syndrome (ARDS) is associated with high mortality (up to 46%) despite best standards of supportive care.[1] One of the major determinants of mortality in severe ARDS is hemodynamic instability and in particular pulmonary vascular dysfunction and right ventricular (RV) dysfunction/failure; [2, 3] however, cardiopulmonary interactions in the context of ARDS are not fully understood. In most ARDS studies RV failure is defined as 'acute cor pulmonale' (ACP) which refers to an abrupt increase in RV afterload. On echocardiography this is characterized by septal dyskinesia and RV dilatation with a ratio of RV end-diastolic area (RVEDA) to left ventricular end-diastolic area (LVEDA) > 0.6 and > 1 for severe ACP.[4, 5] A recent risk score developed for the prediction of ACP in ARDS demonstrated several important clinical and physiological parameters: a) pneumonia as a cause of ARDS; b) ratio of arterial oxygen partial pressure to fractional inspired oxygen (P_aO_2/F_iO_2) < 150mmHg; c) arterial carbon dioxide partial pressure (P_aCO_2) > 48mm Hg; and d) driving pressure > 18cm H_2O.[5] The aforementioned variables have a statistically significant correlation with development of ACP with a reported incidence of 19%, 34% and 74% in ARDS patients with risk scores of 2, 3, and 4 respectively.[5]

Pathophysiology of RV injury in ARDS

Pulmonary vascular dysfunction and RV injury is characterized by increased pulmonary vascular resistance [PVR], pulmonary hypertension, and uncoupling between the RV and pulmonary circulations. ARDS-related pathophysiological factors contributing to this include: hypoxic/hypercapnic pulmonary vasoconstriction; imbalance of vasoactive mediators (eg increased endothelin-1 levels) and increased vasomotor tone; development of intravascular microthrombi; extrinsic vessel compression (due to reduction in lung volume,

interstitial edema and atelectasis); and pulmonary vascular remodelling.[6-8] Factors related to mechanical ventilation and pulmonary mechanics with a negative impact on RV function in ARDS (alveolar vessel collapse leading to increased RV afterload) are: extremes of lung volume and imbalance between overdistension and recruitment; [9-13] plateau pressure (alveolar end-inspiratory pressure) > 27 cmH_2O; [13] and driving pressure (plateau pressure minus total positive end-expiratory pressure) > 18 cmH_2O. [3, 5]

RV function during Prone Ventilation – Evaluating the Evidence

Correction of hypoxemia/hypercapnia along with pressure and volume limited mechanical ventilation could potentially minimize the adverse heart-lung interactions in ARDS. Prone mechanical ventilation has been used as a strategy to improve oxygenation and respiratory mechanics in the most severe form of ARDS (P_aO_2/F_iO_2 < 150mm Hg) when conventional modes of ventilation fail. Early randomized trials showed a consistent association between prone ventilation and improvement in gas exchange but no clear mortality benefit.[14-16] One might argue that this is due to the fact that proning sessions were of short duration (6-8 hours), ventilatory strategies used were non-protective and there was supine/prone cross over.[14-16] Vieillard-Baron et al, examined the effect of prone ventilation on RV function, using transesophageal echocardiography (before and after the first 18-hour session of proning) in 42 patients with severe ARDS (defined as P_aO_2/F_iO_2< 100mm Hg).[17] Acute cor pulmonale was present in 50% of the cohort and prone position ventilation was associated with a significant reduction in plateau pressure and P_aCO_2, with and associated improvement in RV function (reduced RVEDA/LVEDA ratio and septal dyskinesia).[17] Joswiak et al, showed that in patients with moderate to severe ARDS receiving pressure limited low tidal volume ventilation, who are preload dependent, proning was associated with a decrease in RV afterload, increased cardiac index and significant reduction in RVEDA/LVEDA ratio.[18]

The PROSEVA (Proning Severe ARDS patients) randomized controlled trial demonstrated that proning patients with a P_aO_2/F_iO_2< 150mm Hg subjected to low tidal volume ventilation and neuromuscular blockade, confers significant mortality benefit (16.8% absolute reduction in 28-day all cause mortality compared to the supine group).[19] The 'prone ventilation' arm of PROSEVA had fewer cardiac arrests and more cardiac failure-free days at 28 days after recruitment, which could suggest that the 'RV-protective' effect of proning may contribute to survival benefit. Five systematic reviews and meta-analyses based on individual or grouped data from randomized controlled trials (including PROSEVA) have shown that patients with moderate to severe ARDS are likely to benefit from early prone positioning; none of the studies, however, explored cardiovascular outcomes.[20-24] The recently published APRONET (ARDS Prone Position Network) [25] study is the first multicentre international prospective prevalence study dedicated specifically to use of prone positioning. APRONET enrolled 735 ARDS patients (Berlin definition) [26] from 20 countries (141 intensive care units) and showed that 32.9% of severe ARDS patients are being proned. Prone ventilation is associated with significant improvement in gas exchange and a decrease in driving pressure, known to be a risk factor for ACP and an independent predictor of mortality in ARDS.[1, 5, 27] Of note, the two main reasons for not proning patients in the APRONET study were: a) hypoxemia being not severe enough to justify prone positioning, based on the clinicians' judgment (P_aO_2/F_iO_2< 150mm Hg had the lowest odds ratio for predicting the risk for not proning); and b) hemodynamic instability.[25] The latter suggests that intensive care specialists may not be aware that changes in cardiovascular physiology associated with prone position in ARDS are advantageous and in particular reversal of RV-pulmonary artery (PA) uncoupling and RV unloading during prone positioning could potentially confer mortality benefit. [17, 18] However, a major concern remains that it may be difficult for intensivists to distinguish between ACP

and other potential mechanisms of circulatory failure, such as vasodilatory shock as seen in sepsis. This dilemma highlights the value of critical care echocardiography in this setting.

In cases of ARDS complicated by refractory hypercapnia despite prone ventilation, extracorporeal devices could be considered to mitigate the deleterious effects of hypercapnia on the RV (increased RV afterload and RV-PA uncoupling). In particular, extracorporeal veno-venous CO_2 removal ($ECCO_2R$) offers CO_2 clearance and facilitates 'ultraprotective' ventilation (tidal volume of 4ml/kg predicted body weight and reduction in plateau pressure).[28] In an experimental porcine ARDS model, Morimont et al, showed that institution of $ECCO_2R$ effectively reduced hypercapnia during protective ventilation, it reduced PVR and mean PA pressure, and improved RV-PA coupling.[29] However, given the experimental and observational nature of current evidence pertaining use of $ECCO_2R$, it cannot be recommended as an accepted therapeutic measure or routine adjuvant therapy to prone ventilation in ARDS and RV protection at this time. [30]

Feasibility and safety of prone positioning for ARDS in the context of cardiothoracic surgery has not been tested in randomized controlled trials. In fact, two of the PROSEVA trial exclusion criteria were: recent sternotomy and lung transplantation.[19] Retrospective data suggests that prone positioning can be safely applied as a bridge to recovery in lung transplantation recipients with refractory hypoxemia secondary to primary graft dysfunction, and it is associated with a decrease in vasoactive drug support. [31] A proportion of lung transplant candidates have preoperative RV dysfunction/failure secondary to chronic lung disease which may be worsened by perioperative ARDS. [32] It would therefore stand to reason that prone ventilation is considered in this cohort of patients.

Mechanisms of RV unloading during Prone Positioning in ARDS

The physiological effect of prone positioning on the RV and pulmonary circulation can be explained by the following potential mechanisms:

Reduction in Pulmonary Vascular Tone: The ventral-dorsal transpulmonary pressure difference is reduced during prone positioning and as ventilation becomes more homogeneous and the distribution of perfusion remains constant (in supine and prone positions), intrapulmonary shunt decreases and oxygenation improves.[33] The homogenous pulmonary aeration during proning leads to reduced regional stress and strain and better carbon dioxide clearance.[33] The reduction in hypoxic/hypercapnic pulmonary vasoconstriction results in decreased PVR, a decrease in RV afterload and improved RV- PA coupling .[33, 34]

Reduction in Driving Pressure: Driving pressure, a currently used surrogate for dynamic lung stress, can be calculated as the difference between plateau pressure (end-inspiratory alveolar pressure) and total positive-end expiratory pressure (PEEP), and reflects the pressure generated in the respiratory system by the tidal volume.[27, 35] It has been shown that when high PEEP is applied during prone ventilation, the associated reduction in tidal hyperinflation and alveolar cyclic recruitment/derecruitment results in a reduction in driving pressure [36] a reduction in pulmonary capillary and extra-alveolar vessel compression, and a drop in PVR.[12]

Increase in Central Blood Volume: During prone ventilation there is an increase in central blood volume due to shift of blood from the splanchnic into the thoracic circulation which may induce recruitment of pulmonary microvasculature, increase in pulmonary capillary wedge pressure (PCWP) and reduction in PVR and RV afterload.[18, 33] This is probably especially true in patients with preliminary relative or absolute hypovolemia.

Protection against ventilator-induced lung injury (VILI): Injurious mechanical ventilation can further exacerbate RV dysfunction in ARDS. It is assumed that cyclic interruption and exaggeration of pulmonary blood flow during 'high pressure' ventilation may cause pulmonary microvascular injury leading to cor pulmonale. [36] Recent data suggests that not only the RV is the consequence of VILI but it could also promote in part such a VILI.[37, 38] The protective effect of proning against VILI could potentially be explained by ventilatory homogeneity, decrease in tidal hyperinflation, and homogenous distribution of strain.[33-37]

In conclusion, a substantial body of evidence supports the pivotal role of prone positioning in reducing mortality outcomes in severe ARDS. RV failure is a predictor of mortality in ARDS and therefore monitoring and protecting the RV should be made an integral part of a 'heart and lung' protective strategy in severe ARDS. The recommended RV-protective ventilatory goals (driving pressure < 18cmH_2O, P_aCO_2 < 48mmHg and P_aO_2/F_iO_2 > 150mmHg)[5,11] could be met with prone ventilation and no need for recruitment maneuvers and titrated high PEEP, recently found to be associated with mortality.[39] Adequately powered and well-designed randomized controlled trials should test the hypothesis that proning ARDS patients with severe RV dysfunction regardless of P_aO_2/F_iO_2 ratio improves patient-centred outcomes.

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